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ORIGINAL ARTICLE

Iron(III) phosphate catalyzed synthesis of 1,4-dihydropyridines

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Abstract Novel 1,4-dihydropyridines (1,4-DHPs) are prepared efficiently via Hantzsch reaction using aldehydes, benzylacetoacetate and catalytic amount of iron(III) phosphate under solvent-free conditions in good yields.

1. Introduction

Among six-membered heterocyclic compounds, important constituents that often exist in biologically active natural products and synthetic medicinal compounds, are 1,4-dihydropyridines (1,4-DHPs) which are utilized in important biological systems such as acaricidal, insecticidal, bactericidal and herbicidal activities (Khadilkar and Borkar, 1998) and so cardiovascular agents derived from dihydropyridine compounds such as nifedipine, nicardipine, and amlodipine, are effective for the treatment of hypertension, (Buhler and Kiowski, 1987; Reid et al., 1985) and analogues of NADH coenzymes, which have been explored for their calcium channel activity. These heterocyclic rings are found in a variety of bioactive compounds such as bronchodilator, antiatherosclerotic, antitumor, vasodilator, antidiabetic, geroprotective, and heptaprotective agents (Godfraid et al., 1986; Mannhold et al., 1992). These compounds are possessing different medical functions, acting as neuroprotectants, platelet antiaggregators, cerebral antiischemic agents, and chemosensitizers (Bretzel et al., 1993; Klusa, 1995; Boer and Gekeler, 1995). Due to these reasons, 1,4-DHPs not only have attracted the attention of chemists to synthesize but also represent an interesting research challenge. Since the Hantzsch (Hantzsch, 1888, 1890; Dondoni et al., 2004) synthesis more than a century ago, many procedures have been reported for the synthesis of 1,4-DHPs, such as ammonium carbonate in water, (Tamaddon et al., 2010) and the other references cited therein. However, a number of modified methods under improved conditions have been reported, many of them suffer from drawbacks such as unsatisfactory yields, high temperatures, and harsh reaction condition. Lately, an increasing interest has been focused on the synthesis of 1,4-dihydropyridine due to its significant biological activity (Choi et al., 2010).

Also, iron(III) phosphate has been gained as a versatile catalyst for varying transformation in organic synthesis (Behbahani et al., 2010; Behbahani and Farahani, 2011; Heravi et al., 2006). In this communication, we wish to report a novel synthesis of new derivatives of 1,4-DHPs promoted by the catalytic amount of iron(III) phosphate, aldehydes,

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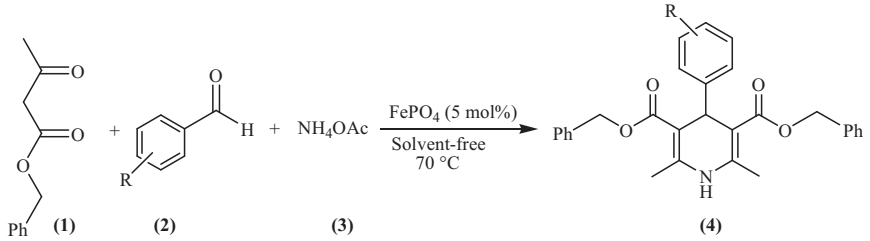


Scheme 1 Synthesis of unprecedented 1,4-dihydropyridines using $FePO_4$.

Table 1 Effect of varying the amount of catalyst on the yield of dibenzyl 2,6-dimethyl-4-(phenyl) 1,4-dihydropyridine-3,5-dicarboxylate.

Entry	$FePO_4$ (mol%)	Time (min)	Yield%[a]
1	15	50	80
2	10	50	80
3	5.0	50	80
4	2.0	120	50
5	Free	120	30

[a] Reaction condition: benzaldehyde (1.0 mmol), benzylacetoacetate (2.0 mmol), ammonium acetate (1.5 mmol) at 70 °C.

benzylacetoacetate and ammonium acetate in one-pot reaction under solvent-free conditions in good yields (Scheme 1).

2. Results

The main goal of this work was to provide a new catalytic and environmentally benign protocol for the synthesis of new derivatives of 1,4-DHPs. At first, in an initial endeavor, benzaldehyde (1.0 mmol), benzylacetoacetate (2.0 mmol) and ammonium acetate (1.5 mmol) were stirred at room temperature under solvent-free conditions. After 5.0 h, 30% of desired product was only realized. To improve the product yields and to optimize the reaction condition, according to our familiarity with iron(III) phosphate in synthesis of heterocyclic compounds (Behbahani et al., 2013) 5.0 mol% of $FePO_4$ was examined using benzylacetoacetate (2.0 mmol), benzaldehyde (1.0 mmol) and ammonium acetate (1.5 mmol) under solvent-free conditions at 70 °C (Table 1). To our surprise, a significant improvement in the yield of the product (80%) was observed (Table 1, entry 1). Thus the catalyst is an efficient component for the synthesis of 1,4-DHPs. Heating of the reaction to 100 °C and reaction duration till 2.0 h did not affect on yield of the product.

3. Discussion

To evaluate the efficiency of iron(III) phosphate as a catalyst, a range of aryl and alkyl aldehydes were subjected to react with benzylacetoacetate and ammonium acetate in the presence of 5.0 mol% of iron(III) phosphate to generate 1,4-DHPs. The results are summarized in Table 2. As listed in Table 2, aromatic aldehydes possessing different substituents such as methoxy, nitro, methyl, chloro and cinnamaldehyde were converted to the corresponding 1,4-DHPs in good yields for short reaction times (50–75 min.).

The aryl group substituted with different groups and same groups located at different positions of the aromatic ring has not shown much effect on the formation of the final product. Protodehalogenation was not observed in any of the reactions studied. Therefore iron(III) phosphate activates the carbonyl group of aldehyde as a Lewis acid in the synthesis of 1,4-DHPs.

4. Experimental

Mps were measured by using the capillary tube method with an electro thermal 9200 apparatus. IR spectra were recorded on a Perkin Elmer FT-IR spectrometer which performed scanning between 4000 and 400 cm^{-1}. ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker DRX-300 MHz NMR instrument in $CDCl_3$. Elemental analyses were performed by an Elemental analyzer Vario EL. Analytical TLC of all reactions was performed on Merck precoated plates (silica gel 60F-254 on aluminum). All starting materials were purchased from Merck Company.

4.1. Synthesis of 1,4-DHPs. general procedure

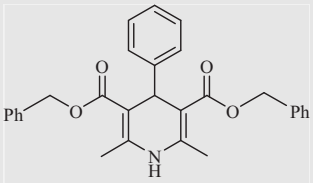
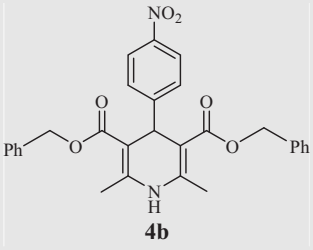
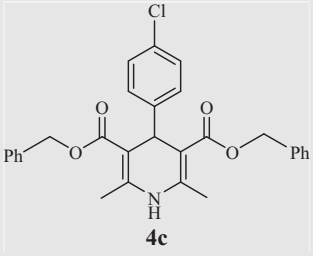
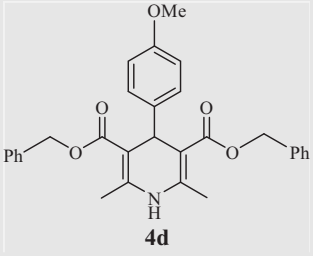
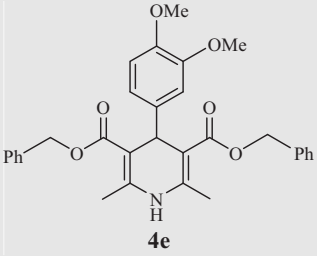
The synthesis was carried out by taking aldehyde (1.0 mmol), benzylacetoacetate (2.0 mmol) and ammonium acetate (1.5 mmol) in a 25 ml round bottomed flask without solvent in the presence of $FePO_4$ (5 mol%) at 70 °C for the required time (Table 1). Progress of the reaction was monitored by TLC (ethyl acetate:n-hexane; 1:8). After completion of the reaction, ethanol (10 ml) was added and the reaction mixture was filtered off for removal of $FePO_4$. Subsequently, ethanol was evaporated and the crude products were separated by column chromatography using ethylacetate: petroleum ether (10:90) mixture and isolated products were characterized by IR, NMR and mass spectroscopy.

After completion of the reaction, $FePO_4$ was filtered, washed by CH_2Cl_2, dried at 50 °C for 1 h and reused for three runs. As it has been shown in Table 3, the reactions were carried out without observation of appreciable loss in catalyst activity.

4.2. Selected physical and spectral data

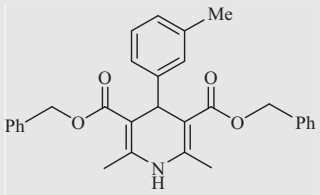
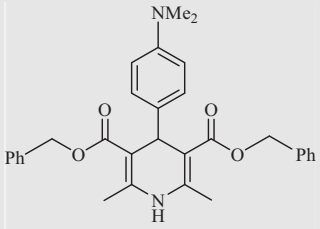
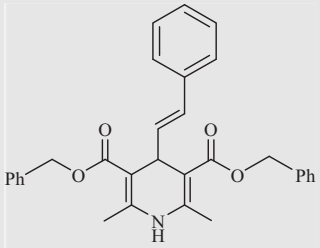
From the reaction of 1 with benzaldehyde, dibenzyl 2,6-dimethyl-4-(phenyl)-1,4-dihydropyridine-3,5-dicarboxylate **4a** (80%) was obtained as a light yellow, oil, IR (KBr, cm^{-1}): 3341.51, 1696.10, 1492.01, 1379.21, 1211.13, 1133.20; ^1H NMR($CDCl_3$, 300 MHz): δ = 2.35 (s, 6H), 5.03 (d, 2H, J = 11.35 Hz), 5.10 (d, 2H, J = 11.35 Hz), 5.37 (s, 1H), 5.70

Table 2 Synthesis of 1,4-dihydropridines using iron(III) phosphate.

Entry	R/aldehyde	Product	Time (min)	Yield%[a]
1	H	 **4a**	50	80
2	4-Nitro	 **4b**	55	80
3	4-Cl	 **4c**	50	77
4	4-OMe	 **4d**	60	80
5	3,4-diMeO	 **4e**	75	77

(*continued on next page*)

Table 2 (continued)

Entry	R/aldehyde	Product	Time (min)	Yield%[a]
6	3-Me	 **4f**	65	75
7	4-NMe_2	 **4g**	70	78
8	Cinnamaldehyde	 **4h**	75	80

[a] Isolated yields.

Table 3 Recycling and reusing of the catalyst have been shown.

Run(s)	Time (min)	Yield%[a]
1	50	80
2	50	80
3	50	77

[a] Reaction condition: benzaldehyde (1 mmol), benzylacetoacetate (2 mmol), ammonium acetate (1.5 mmol), $FePO_4$ at 70 °C.

(brs, 1H), 7.12–7.40 (15H, m); ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 167.2, 149.2, 142.2, 141.2, 129, 125.8, 104.1, 68.9, 43.2, 16.3; GC/MS: 453.19; Elem. Anal. Calcd. for $C_{29}H_{27}NO_4$: C, 76.80; H, 6.00; N, 3.09; Found C, 76.70; H, 6.00; N, 3.01.

From the reaction of 1 with 4-nitro benzaldehyde, dibenzyl 2,6-dimethyl-4-(4-nitrophenyl)1,4-dihydropyridine-3,5-dicarboxylate **4b** (80%) was obtained as a light yellow, oil, IR (KBr, cm^{-1}): 3412.65, 1693.75, 1646.79, 1515.79, 1480.93, 1378.16, 1201.19, 1136.28; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.36 (s, 6H), 4.99 (d, 2H, J = 12.32 Hz), 5.09 (d, 2H, J = 12.32 Hz), 5.40 (s, 1H), 5.77 (brs, 1H), 7.19 (d, 2H, J = 8.57 Hz), 7.27–7.31(10H, m), 7.92 (d, 2H, J = 5.87); ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 167.2, 149.2, 148.3, 145.4, 142.2, 141.2, 129, 121, 104.1, 68.9, 43.2, 16.3; GC/MS: 498.18; Elem. Anal. Calcd. for $C_{29}H_{26}N_2O_6$: C, 69.87; H, 5.26; N, 5.62; Found C, 69.81; H, 5.20; N, 5.58.

From the reaction of 1 with 4-chloro benzaldehyde, dibenzyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **4c** (77%) was obtained as a light brown, oil, IR (KBr,cm^{-1}): 339.00, 1694.38, 1619.26, 1518.02, 1488.67, 1379.05, 1212.04, 1192.33; ^1H NMR($CDCl_3$, 300 MHz): δ = 2.30 (s,6H), 5.03 (d, 2H, J = 11.99 Hz), 5.11 (d, 2H, J = 11.99 Hz), 5.41(s,1H), 5.71(brs, 1H), 7.24–7.27 (d, 2H, J = 8.61), 7.28–7.39 (m, 10H), 7.42 (d, 2H, J = 8.61); ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 167.2, 149.2, 141.3, 140.4, 130.5, 129, 104.1, 68.9, 43.2, 16.3; GC/MS: 487.16; Elem. Anal. Calcd. for $C_{29}H_{26}ClNO_4$: C, 71.38; H, 5.37; Cl, 7.27; N, 2.87; Found C, 71.23; H, 5.27; N, 2.84.

From the reaction of 1 with 4-methoxy benzaldehyde, dibenzyl 4-(4-methoxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **4d** (80%) was obtained as a light yellow, oil, IR (KBr, cm^{-1}): 3327.76, 1698.69, 1644.63, 1588.60, 1508.18, 1494.60, 1374.62, 1201.79, 1133.28; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.32(s, 6H), 3.80 (s, 3H), 5.05 (d, 2H, J = 12.91 Hz), 5.12 (d, 2H, J = 12.91), 5.38 (s, 1H),

5.76 (brs, 1H), 6.69 (d, 2H, J = 9.36), 7.11 (d, 2H, J = 9.36), 7.23–7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 167.2, 157.7, 149.2, 141.3, 140.4, 134.5, 129, 104.1, 68.9, 55.9, 43.2, 16.3; GC/MS: 483.2; Elem. Anal. Calcd. for $C_{30}H_{29}NO_5$: C, 74.52; H, 6.04; N, 2.90; Found C, 74.48; H, 6.02; N, 2.92.

From the reaction of 1 with 3,4-dimethoxy benzaldehyde, dibenzyl 4-(3,4-dimethoxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **4e** (77%) was obtained as a light brown, oil, IR (KBr, cm^{-1}): 3353.78, 1692.87, 1645.40, 1513.50, 1487.88, 1381.21, 1205.07, 1157.38, ^{1}H NMR($CDCL_3$, 300 MHz): δ = 2.33 (s, 6H), 3.42 (s, 3H), 3.83 (s, 3H), 5.04 (d, 2H, J = 12.95 Hz), 5.09 (d, 2H, J = 12.95), 5.40 (s,1H), 6.06 (brs, 1H), 6.66 (d, 1H, J = 8.29 Hz), 6.72 (d, 1H, J = 3.7 Hz), 7.05 (dd, 1H, J = 8.29 Hz and J = 3.7 Hz), 7.13–7.43 (10H, m); ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 167.2, 149.2, 141.3, 135.5, 129, 122.4, 115.2, 114.1, 104.1, 68.9, 56.2, 43.5, 16.3; GC/MS: 513.22; Elem. Anal. Calcd. for $C_{31}H_{31}NO_6$: C, 72.50; H, 6.08; N, 2.73; Found C, 72.41; H, 6.01; N, 2.67.

From the reaction of 1 with 3-methyl benzaldehyde, dibenzyl 2,6-dimethyl-4-*m*-tolyl-1,4-dihydropyridine-3,5-dicarboxylate **4f** (75%) was obtained as a light yellow, oil, IR (KBr, cm^{-1}): 3312.23, 1636.78, 1534.09, 1487.77, 1375.47, 1214.21, 1123.05; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.14 (s, 3H), 2.37 (s, 6H), 5.04 (d, 2H, J = 12.4 Hz), 5.12 (d, 2H, J = 12.4 Hz), 5.42(s, 1H), 6.01 (brs, 1H), 6.87–7.07 (m, 2H), 7.23–7.33 (m,10H), 7.40–7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 167.2, 149.2, 142.3, 138.5, 130.8, 129, 127.4, 115.2, 114.1, 104.1, 68.9, 43.5, 24.6, 16.3; GC/MS: 467.21; Elem. Anal. Calcd for $C_{30}H_{29}NO_4$: C, 77.06; H, 6.25; N, 3.00; Found C, 77.00; H, 6.19; N, 2.98.

From the reaction of 1 with dimethylaminobenzaldehyde, dibenzyl 4-(4-(dimethylamino)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **4g** (78%) was obtained as a light brown, oil, IR (KBr, cm^{-1}): 3313.26, 1660.36, 1534.09, 1486.90, 1373.06, 1212.02, 1123.26; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.19 (s, 6H), 3.01 (s, 6H), 5.08 (d, 2H, J = 13.6 Hz), 5.14 (d, 2H, J = 13.6 Hz), 5.41 (s, 1H), 5.80 (brs, 1H), 6.56 (d, 2H, J = 8.34 Hz), 7.09(d, 2H, J = 8.34 Hz), 7.33–7.49 (m, 10H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 167.2, 149.2, 146.6, 141.5, 137.7, 130, 129, 127.2, 114.2, 104.1, 68.9, 43.5, 40.3, 16.3; GC/MS: 496.24; Elem. Anal. Calcd. for $C_{31}H_{32}N_2O_4$: C, 74.98; H, 6.50; N, 5.64; Found C, 74.95; H, 6.44; N, 5.99.

From the reaction of 1 with cinnamaldehyde, (E)-dibenzyl 2,6-dimethyl-4-styryl-1,4-dihydropyridine-3,5-dicarboxylate **4h** (80%) was obtained as a light yellow, oil, IR (KBr, cm^{-1}): 3380.82, 3082.53, 1671.32, 1510.76, 1480.77, 1379.67, 1213.28, 1156.23; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.33 (s, 6H), 4.75 (d,1H, J = 14.59), 5.12 (d, 2H, J = 12.66), 5.24 (d, 2H, J = 2.66), 5.38(1H, s), 5.80 (brs,1H), 6.18(d, 1H, J = 14.59 Hz), 7.17–7.36 (15H, m); ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 167.2, 149.2, 141.2, 135.7, 130.5, 129, 127.7, 121.7, 102.4, 68.9, 29.4, 16.4; GC/MS: 479.21; Elem. Anal. Calcd. for $C_{31}H_{29}NO_4$: C, 77.64; H, 6.10; N, 2.92; Found C, 77.60; H, 6.01; N, 2.87.

5. Conclusion

In conclusion, we have successfully developed an easy, efficient and versatile method for the synthesis of 1,4-DHPs from the reaction of aldehydes, benzylacetoacetate, and ammonium acetate catalyzed by $FePO_4$ at 70 °C. The process does not require the use of any volatile organic solvent, harmful metal catalyst and thus is a simple, environmentally-friendly, and good yielding reaction for the synthesis of 1,4-dihydropyridines via Hantzsch reaction.

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